

Impact of Lead Toxicity on Body Defense

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ABSTRACT

Lead is regarded as a potent occupational toxin and its toxicological manifestations are well known. The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment. Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelting and coal combustion, lead-based paints, lead containing pipes or lead-based solder in water supply systems, battery recycling, grids and bearings, etc. Although lead toxicity is a highly explored and comprehensively published topic, complete control and prevention over lead exposure is still far from being achieved. There is no such level of lead that appears to be necessary or beneficial to the body and no "safe" level of exposure to lead has been found. Lead toxicity is a particularly insidious hazard with the potential of causing irreversible health effects. It is known to interfere with a number of body functions and it is primarily affecting the central nervous, hematopoietic, hepatic and renal system producing serious disorders. Acute toxicity is related to occupational exposure and is quite uncommon. Chronic toxicity on the other hand is much more common and occurs at blood lead levels of about 40–60 ug/dL. It can be much more severe if not treated in time and is characterized by persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma. Young children are particularly vulnerable to the toxic effects of lead and can suffer profound and permanent adverse health effects, particularly affecting the development of the brain and nervous system. Lead also causes long-term harm in adults, including increased risk of high blood pressure and kidney damage. Exposure of pregnant women to high levels of lead can cause miscarriage, stillbirth, premature birth and low birth weight. Young children are particularly vulnerable to lead poisoning because they absorb 4–5 times as much ingested lead as adults from a given source. Moreover, children's innate curiosity and their age-appropriate hand-to-mouth behaviour result in their mouthing and swallowing lead-containing or lead-coated objects, such as contaminated soil or dust and flakes from decaying lead-containing paint. This route of exposure is magnified in children with a psychological disorder called pica (persistent and compulsive cravings to eat non-food items), who may, for example pick away at, and eat, leaded paint from walls, door frames and furniture. Exposure to lead-contaminated soil and dust resulting from battery recycling and mining has caused mass lead poisoning and multiple deaths in young children in Nigeria, Senegal and other countries. Once lead enters the body, it is distributed to organs such as the brain, kidneys, liver and bones. The body stores lead in the teeth and bones where it accumulates over time. Lead stored in bone may be remobilized into the blood during pregnancy, thus exposing the fetus. Undernourished children are more susceptible to lead because their bodies absorb more lead if other nutrients, such as calcium or iron, are lacking. Children at highest risk are the very young (including the developing fetus) and the economically disadvantaged. Lead poisoning occurs when lead builds up in the body, often over a period of months or years. Research indicates about 500,000 U.S. children between the ages of 1 and 5 have blood lead levels above 5 micrograms per deciliter, the reference level at which the CDC recommends public health actions be initiated. Children under the age of 6 are especially vulnerable because their growing bodies absorb more lead than adults and because they tend to put their hands or other objects, which may be contaminated with lead dust, into their mouths. The signs and symptoms of lead poisoning often don't appear until dangerous amounts of lead have accumulated. Even low levels of lead in blood have been shown to affect IQ, the ability to pay attention and academic achievement. At very high levels, lead poisoning can be fatal. The effects of lead exposure cannot be corrected. Lead pollution can also cause irreversible encephalopathy, seizure, coma and even death. Fatigue, memory loss, high blood pressure, nephropathy,

gastrointestinal disturbances, weight loss and immuno-suppression are other common toxic effects of lead exposure in animals. Prenatal exposure to metal may also cause birth defects, miscarriage and underdeveloped babies.

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INTRODUCTION

Lead, a chemical element in the carbon group with symbol Pb (from Latin: Plumbum, meaning "the liquid silver") and has an atomic number 82 in the periodic table. It was the first element that was characterized by its kind of toxicity. In animal systems, lead (Pb) has been incriminated in a wide spectrum of toxic effects and it is considered one of the persistent ubiquitous heavy metals. Being exposed to this metal could lead to the change of testicular functions in human beings as well as in the wildlife. The lead poisoning is a real threat to the public health, especially in the developing countries. Accordingly, great efforts on the part of the occupational and public health have been taken to curb the dangers of this metal. Hematopoietic, renal, reproductive, and central nervous system are among the parts of the human body and systems that are vulnerable toward the dangers following exposure to high level of Pb. In this review, we discussed the massive harmful impact that leads acetate toxicity has on the animals and the worrying fact that this

harmful toxicant can be found quite easily in the environment and abundance. Highlighting its (Pb) effects on various organs in the biological systems, its economic, as well as scientific importance, with the view to educate the public/professionals who work in this area.[1]

Acute lead poisoning can present with severe symptoms of toxicity or with nonspecific signs and symptoms, depending in part on how much lead has been absorbed. In addition, chronic exposure to modest or even low levels of lead may produce no symptoms but increase the risks for long-term development of adverse health outcomes.

The consequences of lead exposure may be reduced by taking an occupational and environmental health history, recognizing the early symptoms of elevated blood lead levels (BLL) and lead poisoning, having a low threshold for suspecting asymptomatic lead exposure based on an occupational and environmental history or medical findings, and checking BLL in such cases to verify the diagnosis and provide appropriate advice and treatment.

Lead exposure is arguably the oldest known occupational health hazard. It is a particularly insidious hazard with the potential for causing irreversible health effects, including hypotension, central nervous system problems, anemia and diminished hearing acuity before it is clinically recognized. Scientific evidence of subclinical lead toxicity continues to accumulate, making further reduction in workplace exposure, regular screening, and earlier diagnosis and treatment of critical importance in the prevention of this occupational hazard. Lead is absorbed primarily through the respiratory and gastrointestinal systems, with the former being the more important route of entry in occupational exposures. Cutaneous absorption of inorganic lead is negligible. However, organic lead compounds, because of their lipid solubility, are readily absorbed through intact skin. Respiratory lead absorption is primarily dependent on particle size; solubility, respiratory volume and physiologic interindividual variation are less important factors. The percentage of inhaled lead reaching the bloodstream is estimated to be 30 to 40 percent. Gastrointestinal absorption of lead is lower in adults than in children, with an estimated 10 to 15 percent of lead in an adult's diet absorbed gastrointestinally. The degree of lead absorption is increased considerably with fasting or in persons whose diet is deficient in calcium, iron, phosphorus or zinc.[2]

DISCUSSION

With chronic exposure over a long period of time, most absorbed lead ends up in bone. Lead, it appears, is substituted for calcium in the bone matrix. This is not known to cause any deleterious effect on bone itself. Bone storage likely acts as a "sink," protecting other organs while allowing chronic accumulation. The lead that accumulates in the bone ultimately provides a source for remobilization and continued toxicity after exposure ceases. Although lead is excreted by several routes (including sweat and nails), only the renal and gastrointestinal pathways are of practical importance. In general, lead is excreted quite slowly from the body (with the biologic half-life estimated at 10 years). Since excretion is slow, accumulation in the body occurs easily. The diagnosis of inorganic lead intoxication in adults requires the demonstration of excess lead absorption, documentation of impairment in an organ system consistent with the effects of lead, and exclusion of other causes of disease. At present, the blood level concentration is the

single best indicator of recent, acutely elevated lead absorption. This level provides good information on lead absorption in persons with relatively brief exposure, such as construction workers or new entrants into the lead industry. The blood lead level rises rapidly within hours after an acute exposure and remains elevated for several weeks. A single case of occupational lead poisoning may represent a "sentinel health event," thereby serving as a warning of potential overexposure of other workers. [3]

With the assistance of industrial hygiene experts, the patient's workplace should be investigated for possible additional cases and causes. State health departments should be notified with possible referral to an occupational medicine specialist if questions remain regarding treatment protocol, worker disposition and work-place evaluation. *in vitro*, lead exposure enhances both B cell and T cell production and major histocompatibility complex (MHC) activity. *In vivo* and *ex vivo* animal studies and studies *in vitro* show that lead can activate responses mediated by T helper 2 (Th2) cells and suppress the production of Th1 cells (42). Th cells represent two polarized forms of the CD4+ Th cell-mediated specific immune responses, helper cells can be divided into distinct subsets, including Th1, Th2, Th17 and T regulatory (Treg) cells. However, the effects of lead exposure on the human immune system are not conclusive, mostly in occupationally exposed subjects; nevertheless some immunotoxic abnormalities induced by lead have been suggested. Probably the immunotoxic effects of lead vary according to form of lead, route, dose, time of exposure, and host age and genetic susceptibility.[4]

RESULTS

Lead is a ubiquitous environmental toxin that is capable of causing numerous acute and chronic illnesses. Population studies have demonstrated a link between lead exposure and subsequent development of hypertension (HTN) and cardiovascular disease.[19] *In vivo* and *in vitro* studies have shown that chronic lead exposure causes HTN and cardiovascular disease by promoting oxidative stress, limiting nitric oxide availability, impairing nitric oxide signaling, augmenting adrenergic activity, increasing endothelin production, altering the renin-angiotensin system, raising vasoconstrictor prostaglandins, lowering vasodilator prostaglandins, promoting inflammation, disturbing vascular smooth muscle Ca²⁺ signaling, diminishing endothelium-dependent vasorelaxation, and modifying the vascular response to vasoactive agonists. Moreover, lead has been shown to cause endothelial injury, impede endothelial repair, inhibit angiogenesis, reduce endothelial cell growth, suppress proteoglycan production, stimulate vascular smooth muscle cell proliferation and phenotypic transformation, reduce tissue plasminogen activator, and raise plasminogen activator inhibitor-1 production. Via these and other actions, lead exposure causes HTN and promotes arteriosclerosis, atherosclerosis, thrombosis, and cardiovascular disease. In conclusion, studies performed in experimental animals, isolated tissues, and cultured cells have provided compelling evidence that chronic exposure to low levels of lead can cause HTN, endothelial injury/dysfunction, arteriosclerosis, and cardiovascular disease. [5]

More importantly, these studies have elucidated the cellular and molecular mechanisms of lead's action on cardiovascular/renal systems, a task that is impossible to accomplish using clinical and epidemiological investigations

alone. Lead is absorbed via the respiratory and gastrointestinal tracts and, occasionally, through the skin. [17,18] Lead absorption via the respiratory tract is highly efficient, resulting in an average uptake of 40% of the inhaled lead. The dominant route of exposure through the lung in adults is associated with smelting and burning processes, as well as inhalation of lead-containing dust from scraping, burning, or sanding lead paint from surfaces, as well as exhaust from vehicles and planes powered by lead-containing gasoline. The gastrointestinal tract is less efficient, with ~10–15% of the ingested lead being absorbed. In addition, tetraethyl lead, a previously common gasoline additive, is absorbed via the cutaneous route. After absorption, lead is distributed in the blood, bone, and soft tissues. Approximately 99% of blood lead content is bound to red blood cells; only 1% is present in the plasma and is available for exchange with lead contained in the other tissues. The half-life of lead in the blood is ~30 days in individuals with normal renal function and longer in those with renal insufficiency.[6]

Erythrocytes have a high affinity for lead, binding 99 percent of the lead in the bloodstream. Lead has a destabilizing effect on cellular membranes, and in red blood cells (RBC) the effect decreases cell membrane fluidity and increases the rate of erythrocyte hemolysis. Hemolysis appears to be the end result of ROS-generated lipid peroxidation in the RBC membrane. Lead can also bind directly to phosphatidylcholine in the RBC membrane, leading to a decrease in phospholipid levels. Hypochromic or normochromic anemia is a hallmark of lead exposure; it results from ROS generation and subsequent erythrocyte hemolysis. Lead is considered, along with silver, mercury, and copper, to be a strong hemolytic agent, able to cause erythrocyte destruction through the formation of lipid peroxides in cell membranes. In addition to membrane peroxidation, lead exposure causes hemoglobin oxidation, which can also cause RBC hemolysis. [7]

Lead-induced oxidative stress has been identified as the primary contributory agent in the pathogenesis of lead poisoning. Oxidative stress has also been implicated in specific organs with lead-associated injury, including liver, kidney and brain tissue. ROS (reactive oxygen species) generated as a result of lead exposure have been identified in lung, endothelial tissue, testes, sperm, liver and brain. The reactive oxygen species generated by lead is responsible for the ovarian dysfunction affecting the female reproduction. The ovarian follicle is the functional unit of the ovary. It contains the oocyte that may eventually ovulate, undergo fertilization and form an embryo. It also provides the steroid and protein hormones required for maintenance of the ovarian cycle, the secondary sex characteristics and preparation of the uterus for implantation. Lead-induced changes in the circulatory system affect the occurrence of cardiovascular end points in lead exposed populations. [15,16] Intermediate indicators of these events are functional and structural changes in the heart, such as changes in the left ventricular mass, heart rate, heart rate variability or electrocardiographic abnormalities. The 24-hour electrocardiographic evaluation performed in our centre in groups of men occupationally exposed to lead (copper foundry workers) showed that various heart rhythm disorders were more frequent as compared to the controls. In a group of men with arterial hypertension, occupationally exposed to lead, the study has demonstrated a significantly

more frequent manifestation of left ventricular diastolic dysfunction and an increase in local arterial stiffness. [8]

Some of the critical effects of lead result from lead interference with enzymatic processes responsible for the synthesis of heme. These include the inhibition of delta-aminolevulinic acid dehydratase (ALAD), changes in the concentration of delta-aminolevulinic acid in urine (ALA-U), blood (ALA-B) or plasma (ALA-P), changes in the concentration of coproporphyrin in urine and zinc protoporphyrin (ZP) in blood. As a result of exposure to lead, there is a decrease in activity of blood pyrimidine nucleotidase (P5'N) and nicotinamide adenine dinucleotide synthetase (NADS), as well as changes in nucleotides' blood content. All these effects have been used as biomarkers of lead toxicity. In vitro studies demonstrated that the treatment of macrophages with lead induces the dysregulation of the production of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 α (IL-1 α) and IL-6, and promote the synthesis of Th1 cytokines [interferon (IFN)- γ and IL-2][9,10]

CONCLUSION

The first step of treatment is to locate and remove the source of the lead. Keep children away from the source. If it cannot be removed, it should be sealed. Call your local health department for information on how to remove lead. They can also help you reduce the likelihood of lead exposure. In more severe cases, a procedure known as chelation therapy can be used. This treatment binds to lead that has accumulated in your body. The lead is then excreted in your urine. Chemical chelators that are used most often include EDTA and DMSA. EDTA has side effects that include kidney dysfunction, and DMSA can often cause nausea, abdominal distress, and allergic reactions, among others. Even with treatment, it can be hard to reverse the effects of chronic exposure. Prevention methods are:

- Avoid or throw away painted toys and canned goods from foreign countries.
- Keep your home free from dust.
- Use only cold water to prepare foods and drinks.
- Make sure everyone washes their hands before eating.[11,12]
- Test your water for lead. If lead levels are high, use a filtering device or drink bottled water.
- Clean faucets and aerators regularly.
- Wash children's toys and bottles regularly.
- Teach your children to wash their hands after playing.
- Make sure any contractor doing work in your house is certified in lead control.
- Use lead-free paint in your home.
- Take young children for blood lead level screening at their pediatrician's office. This is usually done around 1 to 2 years of age.
- Avoid areas where lead-based paint may have been used.

It is well-established that exposure to lead can promote the development of several diseases and disorders through different mechanisms of toxicity. The hypothesis that the immune system represents a critical target for lead-induced

toxicity has been suggested by recent epidemiological and experimental studies. In particular, lead can affect both cellular and humoral immune response by altering Th cell function and increasing susceptibility to the development of autoimmunity and hypersensitivity. In the context of hypersensitivity, the use of cyclophosphamide may affect the immune response by reducing the expression levels of several cytokines as occurred in our previous in vivo experience. A great number of epidemiological and experimental studies are available, but results are often contradictory because of some limitations, such as the presence of possible confounding factors, the size of the samples, the dose and time of exposure to lead, and the use of safety measurement in occupational environment. Furthermore, few studies evaluated the effects of lead exposure on subjects occupationally exposed to low-dose of lead. Further studies are needed in order to investigate the mechanisms of lead immunotoxicity and the ability of lead to affect preferentially one type of immune response.[13,14]

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